REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Office Action dated September 12, 2007. In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Applicants gratefully acknowledge the opportunity to discuss claim 36 with the Examiner on March 04, 2007 and believe that the foregoing amendments, in light of the Examiner's concerns, will greatly advance the prosecution of this Application. Applicants are grateful for the Examiner's time and attention. .

Status of the Claims

Claims 36-39 and 41 - 68; stand for consideration in this application, wherein claims 1-35, 40, stand canceled without prejudice or disclaimer, while claims 45 -66 stand withdrawn and claim 36 is being amended to more particularly point out and distinctly claim the subject matter of the invention.

Support for step a) may be found on page 6, ¶ 2; for step b) on page 19 ¶ 4; for step b on page 6, ¶ 2; for step d) on page 17, ¶ 1; for step e) on page 11 ¶ 4; for step f) on page 9 ¶ 4; for step g) on page 5 ¶ 4, page 6, ¶ 1, page 12 ¶ 2; and step h) page 12, ¶ 1.

Rejections under 35 U.S.C. 112, Second Paragraph

Claims 36 – 39, 41-44, 67, and 68 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

The Examiner alleges that it was unclear whether the phrase, "interlockingly connected *in vitro*" to each other was a product limitation and how it changed the scope of the claims. As amended, claim 36 is now in a proper product-by-process format and now explicitly recites an interlocking area being the mating ends of the joint side and the anchor side. As explicitly stated in the specification on page 5, paragraph 4 and on page 6, paragraph 1, the mating ends of the joint side and the anchor side are configured to interlock,

preferably in an interdigitating manner. Further, as explicitly stated on page 12, paragraph 1:

> It is essential to the invention that during the connection of bone and cartilaginous component, the carrier material of the bone component is integrated into the cartilage. The resulting construct can now be cultured in vitro, such that the cells are stimulated to adhesion and to the synthesis of their tissue-specific extracellular matrix.

Page 12, paragraph 1. The interlocking area, being as it were, an essential embodiment of the present invention, it is expected that it be accorded all the patentability weight inherent therein.

The Examiner also required clarification as to how the first and the second biocompatible materials relate to the overall physical and structural configuration of the claimed product. As described on page 3, paragraph 2, page 3, paragraph 4, and page 4, paragraph 5, the carrier materials for the cartilaginous side and the bone side are preferably and not necessarily the same biomaterial. In the embodiment claimed, the carrier materials are physically and structurally distinct between the bone side (anchor side) and the cartilaginous side (joint side). As for whether the cells are cultured on these biomaterials, it is believed that the process steps have made that clarification as is further evinced by the description on page 12, paragraph 1. It is also believed that the clarification and the rendering of claim 36 as a product by process claim have obviated the Examiner's concerns with respect to claim 68, being that fibrin adhesion as described in the specification is a means for ensuring the connection and integration of the biocarriers on both sides.

On the basis of the foregoing, Applicants respectfully request the withdrawal of this ground for rejection.

Rejections under 35 U.S.C. 103(a)

Claims 36, 38, 41, 42, 44, 67 and 68, stand rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Itay (U.S. 5, 053, 050), in view of Mikos (1996 US Patent 5,522,895; reference A), Rosenthal et al. (1995, U.S. Patent 5, 466, 462, reference B), and Jakob et al. (WO 99/21497; and German-to-English translation).

The Examiner admits that Itay does not teach an *in vitro* composition comprising both cultured cartilage cells and cultured bone cells, said composition comprising cartilage cells on one face thereof and bone cells on the opposing face. The Examiner asserts, however, that Mikos teaches seeding osteoblasts in growth medium onto a biodegradable polymer, allowing the suspension to wick into the polymer foam, and culturing the cells on the polymer to allow them to attach to the foam.

The Examiner further asserts that Rosenthal *et al.* teach that fibrin and polyglycolic acid are functional equivalents in the tissue engineering and wound healing arts.

The Examiner further asserts that Jakob *et al.* teach a composition comprising both a bone side and a cartilage side; the composition of Jakob et al. being a column of tissue that has been removed from a donor site at the articular face of a bone. The Examiner further asserts that Jakob et al. also teach a composition comprising cartilage cells cultured *in vitro* on bone-replacement material.

The Examiner insists that she would construe the transitional phrase, "consisting essentially of" as the open-ended phrase, "comprising" unless the Applicants show that introduction of additional steps or components would materially change the characteristics of Applicants' invention.

The Examiner further claims that the description on page 5 of the specification regarding the definition of "cartilaginous substance" and "bone substance" are not limiting and in the Examiner, words, "include all non-cellular components of cartilage and bone respectively."

The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the *in vitro* bone construct of Mikos and the *in vitro* cartilage construct of Itay to yield a composition comprising cultured cartilage on one side and cultured bone on the opposite side because Jakob *et al.* teach that compositions so configured may be implanted into the articular portions of bones to effectively treat defects. Applicants respectfully disagree and now traverse as follows.

Applicants strongly disagree with the propriety of the combination asserted above by the Examiner. The Examiner is arguing that natural tissue grafting as taught by Jakob et. al., obviates as uninventive, any attempt to generate biocompatible tissue or organ *in vitro* merely because the cells that could form part of that *in vitro* tissue or organ have been separately cultured at some point by others. In that sense, why should inventors labor in the field of tissue engineering only for the Examiner to point out that the natural tissue has vitiated their efforts, whereas the main object of such endeavor is to attempt to generate artificial tissue *in vitro?* Naturally the functionality and structure of the natural tissue motivates such endeavor, but that is not the relevant inquiry for patentability purposes; the inquiry is whether a functional joint can be generated *in vitro* and not whether the resulting product looks like the real thing. It is to Applicants' inventive credit, not to their discredit, that their artificial joint mimics Jakob's *et al.'s* natural bone graft. Applicants believe that they were not only the first to do so, but the difficulties in culturing animal cells in the laboratory make the ability to construct a biological joint wholly *in vitro* a highly inventive undertaking.

If the artificial joint looks like the real thing, it is the very inventive genius which Applicants are seeking protection for. After all, it is one of the objects of the instant invention to generate joint-mimetic construct *in vitro* and the ultimate object is to engineer one as close in

structure and function to a natural joint as possible. Thus, the relevant inquiry is whether Jakob *et al.* and other cited references in anyway teach, suggest, motivate, or else point to the likelihood of success of an attempt to engineer a functional biological joint *in vitro.*

Nor do the Applicants contend that they are the first to culture bone cells or cartilage cells. Nor do the Applicants suggest that they are the first to realize that animal cells in general are anchorage dependent. Applicants contend, however, that they are the first to culture anchorage dependent osseous and cartilaginous cells suitably anchored on biocompatible materials and arranged in such a manner as to constitute a novel and unobvious joint construct.

As now amended, Applicants' *in vitro* joint construct comprise a joint side, an anchor side, and an interlocking zone for effecting an *in vitro* integration of both sides in order to *in vitro* create the functional equivalent of a joint. Support for the interlocking zone may be found in the last paragraph of pages 5 and 11; and Figures 1f and 1g.

Thus, although Applicants believe that anchorage-dependent cartilage and osseous cells may have been grown by others before the date of this invention, Applicants do not believe that a natural organ or tissue being composed of cells provide motivation to preclude the inventiveness of a wholly *in vitro* joint construct aimed at generating in the laboratory, an organ or tissue as close to the natural organ as possible. And even if it were so, the *in vitro* construct of the instant invention differs in material structural respects from the natural joint. For one thing, the interlocking zone mentioned above is a non-natural feature; for another thing, the nerves, gross histological components, connective tissues, and vascularization of a natural joint are lacking in the artificial joint of the present invention, and whereas the artificial joint of the present invention can be used to effect repair of damaged bone, it is nevertheless a man-made joint and should be regarded as such for patentability purposes.

Nor do the Applicants believe that their interlocking bone-cartilage articulating junction approximate its anatomical counterpart. And neither can it reasonably be asserted that the asserted prior art obviated the inventiveness of finding a way, in vitro, to integrally connect the cartilage side and the osseous side in order to engineer an orthopaedically functional joint construct.

To more distinctly claim the invention as an in vitro joint construct, Applicants have deleted the phrase "cartilaginous substance" and "bone substance" and instead replaced them with "cartilaginous matrix" and "bone matrix," respectively. Part of the difficulty in advancing the prosecution of this invention is the Examiner's insistence on treating the invention as a composition and her requirement that the Applicants should have listed the entire biochemical composition of the cartilaginous matrix or the bone matrix in order to recite "substance" in a

limiting fashion. Applicants are not required to, nor did they attempt to recite the entire histology and gross anatomy of a joint in order for one of skill in this area to appreciate why an in vitro biomimetic joint construct, produced according to the enumerated steps, is fundamentally and inventively different from the natural joint. In very fundamental ways, the process does indeed define the product and the fact that this product is in vitro, without more, patentably separates it from the Jakob construct.

Chondrocytes are the only cells found in cartilage. They produce and maintain the cartilaginous matrix, which consists mainly of collagen and proteoglycans. Applicants believe that there is no other limiting definition of "cartilaginous substance" other than that it consists mainly of collagen and proteoglycans. On the other hand, osteoblasts are mononucleate cell that are responsible for bone formation. Osteoblasts produce osteoid, which is composed mainly of Type I collagen. Osteoblasts are also responsible for mineralization of the osteoid matrix. Bone is a dynamic tissue that is constantly being reshaped by osteoblasts, which build bone, and osteoclasts, which resorb bone.

Regarding the Examiner's insistence that Applicants have not met their burden of showing that they are entitled to the scope-limiting use of "consisting essentially of" because they have not shown the basis and novel characteristics of the claimed composition. Applicants respectfully disagree.

In the Response to Office Action filed January 11, 2007, Applicants went into extraordinary detail to show how and why an in vitro joint construct would be anatomically and compositionally different from a natural joint construct. In this case, the bone side of the present invention consists essentially of osteoblasts and tissue-specific extracellular matrix secreted by such cells. Likewise, the cartilage side of the present invention consists essentially of chondrocytes and tissue-specific extra-cellular matrix secreted by chondrocytes. Contrarily, a natural joint like Jakob et al; consists of a physiologically dynamic bone tissue in which osteoblasts are building bone and osteoclasts are resorbing bone. Namely, the bone side of the present invention does not contain osteoclasts as is evident by the process of its making, and thus assuming that the Examiner's asserted combination were proper to begin with, the said combination still fails to account for all the elements of the present invention.

For the records, Applicants have in no way claimed, as erroneously asserted by the Examiner on Page 9 of the Office action, that their *in vitro* construct is identical to Jakob's in

vivo bone graft. Applicants have claimed that their *in vitro* joint construct is a biomimetic construct designed to approximate a natural joint as functionally and anatomically as possible in a laboratory setting.

On the basis of the foregoing, Applicants assert that there is no basis for maintaining the obviousness rejection of the instant invention and it is respectfully requested that it be withdrawn.

Claim 37 is rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Itay (U.S. 5, 053, 050), Mikos, Rosenthal et al., and Jakob et al. as applied to claims 36, 38, 41, 42, 44, and 67 above, and further in view of Goldstein et al. (1999, U.S. Patent 5,962,427: reference C) and Vacanti et al. (1998, U.S. Patent 5,804,178; reference D). Further, claims 39 and 43 are rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Ithay (U.S. 5, 053, 050), Mikos, Rosenthal et al., and Jakob et al. as applied to claims 36, 38, 41, 42, 44, and 67 above, and further in view of Wevers (1981, U.S. Patent 4,246,660) and Dunn et al. (1995, Journal of Biomedical Materials Research 29:1363-1371).

Claim 37, 39 and 43, being dependent on claim 36, it is respectfully asserted that the foregoing have adequately addressed this ground for rejection or rendered it moot.

Suffice it to state that the genius of an invention is often a combination of known elements that in hindsight seem preordained. It is improper to use the inventor's patent as an instruction book on how to reconstruct the prior art. Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir. 1987). The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the Applicant's disclosure. *In re O'Farrell,* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

Applicants respectfully ask that the Examiner to not let hindsight hamper the elegance of the instant wholly-engineered joint construct, if in retrospect, it appears simple enough to the Examiner. Many a Scientists know and appreciate the difficulties of culturing a monolayer of anchorage dependent animal cells of a particular kind, let alone co-culturing animal cells of more than one kind, let alone doing so in a three-dimensional construct, let alone doing so with a structural articulation as complex as a joint. If this invention were obvious, many would have done it because there is a huge orthopedic need for constructs that would accelerate joint healing without the need to graft orthopedic material taken from a different part of the patient's anatomy.

Again, the mere fact that Scientists have grown cells used in the instant invention in the past does not in anyway render obvious the engineering of an organ or tissue comprising those cells.

The Examiner is respectfully asked to reconsider and withdraw these grounds for rejection particularly for the fact that even if the Examiner insists on making these combinations, the combined art still does not anticipate the invention of claim 36. Particularly, the in vitro integration of the joint and the anchor side of the joint construct renders the resulting artificial construct different from any combination which the prior art would teach. As such, it is again respectfully requested that this ground for rejection be withdrawn.

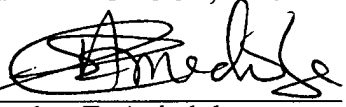
Conclusion

In view of the foregoing remarks, Applicants submit that there is no basis for applying the previous rejections to the pending claims and withdrawal of the rejections is respectfully requested. The claims are believed to be in condition for allowance, and Applicants earnestly solicit from the Examiner early notification of allowability.

Should the Examiner have any questions or believe a personal or telephonic interview may be in order, she is invited to contact the undersigned at her earliest convenience.

Respectfully submitted,

DOBE LAW GROUP, LLC

By: 
Christopher E. Aniedobe
Reg. No. 48,293

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Dobe Law Group, LLC
7207 Hanover Parkway
Suite C/D
Greenbelt, MD 20770
Phone: 301 982 0154
Fax: 301 982 0154
Email: Chris@DobeLawGroup.com